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Variants of SARS-CoV-2, their effects on infection, transmission and neutralization by vaccine induced antibodies

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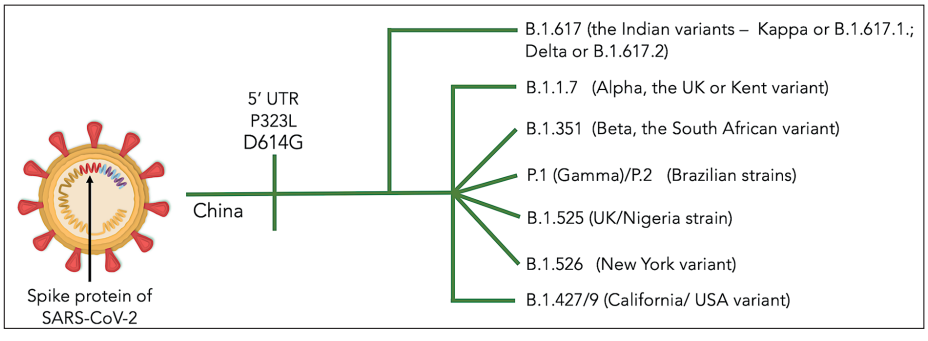
Abstract. – OBJECTIVE: The current study reviewed Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) variants for their effects on infection, transmission and neutralization by vaccine-induced antibodies.

MATERIALS AND METHODS: The research articles for the current study were searched over PubMed, Google Scholar, EMBASE and Web of Science online databases. The keywords used were: [("SARS-CoV-2" OR "COVID-19") AND ("mutation" OR "variant") AND ("death" OR "hospitalization" OR "infection" OR "transmission") AND ("antibody" OR "neutralize" OR "vaccine")]. A total of 333 research articles were retrieved through online-database search. These articles were further scrutinized for their relevancy. Additionally, searches were performed to find the latest relevant information over Google search engine and relevant news browsers. Finally, around 35 germane articles were considered for scripting the current report.

RESULTS: The mutations have changed amino acids at key positions in spike protein viz. S477N, E484K, Q677H, E484Q, L452R, K417T, K417N and N501Y. These mutations are relevant for different characteristics and are present in newly evolved strains of SARS-CoV-2 like E484K in B.1.526, B.1.525, P.2, B.1.1.7, P.1 and B.1.351. Mutations have increased the immune escape potential leading to 3.5-6.5-folds decrease in neutralization of antibodies (Pfizer and Moderna vaccines). The variant, B.1.617 circulating in India and many other countries (double variant) having E484Q and L452R mutations, has raised the infection rate and decreased the neutralization capacity of the vaccine-induced antibodies. Deadly K417N+E484K+N501Y triplet mutations found in B.1.351 and P.1 have increased the transmission ability of these strains by 50% leading to greater COVID-19 hospitalization, ICU admissions and deaths.

CONCLUSIONS: The new SARS-CoV-2 variants have compromised the neutralization potential of the currently used vaccines, but still, they have considerable efficacy to reduce infection and mortality.



Graphical Abstract. Evolution of various SARS-CoV-2 variants.

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Introduction

The viruses change themselves continuously. The changes occur through mutation lead to advent of new variants. These variants can haunt the mankind or may even go unnoticed[1]. Mutations may help the viruses in adapting to unfaithful environments. The viruses undergo mutations at varying pace, for example, RNA viruses show higher rate of spontaneous mutations than DNA viruses[2]. It depends on their *de novo* generation capacity in a very short span of time. Thus, it can be said that higher mutation rates in RNA viruses cause greater genetic diversity, which play a key role in viral evolution[3]. The understanding of viral evolution that occurs through mutation and genetic diversity help in managing the infections and deadly diseases in several efficient ways. The viral diseases can also be managed by understating the drug resistance of viruses, their immune escape ability and response to vaccines[2].

As Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the etiological agent of COVID-19 pandemic, is spreading across the countries, it is continuously changing itself or undergoing genetic variations causing antigenic drift. The antigenic drift may dupe the immune system of the infected person. The antigenic drift might develop as a result of random errors during the replication process. The random errors alter the viral surface protein and may not be recognized by the developing antibodies in naturally infected individuals[4]. The genome of coronavirus is made of a single strand of a long RNA piece. During the infection, two different coronaviruses (CoVs) may infect the same cell of the host. The genome of two CoVs can undergo recombination inside the cell, which may lead to stitching of the two genomes together. This process leads to the development of new CoV strains having potential to wreak havoc during pandemics[4]. However, it is not always necessary that recombination of viral genomes should take place to cause pandemic. The viral genomes may undergo point mutations (missense) very often in their genomes and cause pandemic. Most of the variants of CoVs circulating around the world are formed as a result of point mutations in their nucleotides during replication. For example, two mutations A23403G (S: D614G) and C14408T (ORF1ab: P4715L) are dominantly present in more than 95% genomes of the new viruses spreading across the world[5]. Furthermore, there are various other mutations found in SARS-CoV-2 new variants. These mutations are E484K, N501Y, K417N and L452R, which are extremely significant for their transmission, virulence, antigenicity and evading antibody actions[6]. The new variants are causing serious illness even in children and young age people[7,8]. These new variants have origin in different geographic locations like United Kingdom, South Africa, Brazil, Philippines, United States of America and India.

SARS-CoV-2 Variants' Classification, Origin and Characteristics Features

Several coronavirus variants causing COVID-19 are spreading in different countries. The new variants are proving themselves to be more devastating in terms of mortality, transmission and vaccine evasion (Table I)[9]. These variants have been classified mainly into three groups by the Centers for Disease Control and Prevention (CDC) and SARS-CoV-2 Interagency Group (SIG). These groups are: Variant of Interest (VOI), Variant of Concern (VOC), and Variant of High Consequence (VOHC) (Table I)[10]. These variant groups have many associated attributes such as specific genetic markers, transmission, disease severity, influence of neutralizing antibodies and the effect of these circulating variants on medical countermeasures (MCM)[10].

The main coronavirus variants (Table I), which are being studied and that showed their presence in different countries are:

B.1.526 Variant

It is also known as 20C/S:484K. It was first detected in New York (United States of America) in November-2020. It resists the human immune system as a result of mutation in genetic material. It also leds to the emergence of several versions of SARS-CoV-2. These versions are developed because of mutations which leads to changes in spike protein. These spike proteins act as receptor binding domain (RBD). The important mutations seen in B.1.526 were L5F, T95I, D253G, S477N, E484K, D614G, A701V[11]. Out of these mutations, S477N and D614G attracted the attention of scientists across the globe. S477N mutation changes the spike protein to bind the human cells tightly, whereas E484K helps in the evasion from antibodies. There are reports which shows that the antibodies produced in the human body by vaccination shows good protection for S477N muta-

Table I. Characteristic properties of different SARS-CoV-2 variants found all over the world.

Coronavirus Variant/Lineage	Original Location Year	Current presence	Prominent Mutations (Spike protein)	Transmissibility	Virulence	Antigenicity	Neutralization of coronavirus variant by vaccine/ Efficacy of vaccines			Reference
B.1.526	New York-November 2020	USA and 18 other countries	L5F, T95I, D253G, S477N, E484K, D614G, A701V	Increases	Increases	Decreases	Yes	3.5-fold decrease	Pfizer	(11, 12, 36-38)
							Yes	3.5-fold decrease	Moderna	
B.1.526.1	Now York-October 2020	USA and many other countries	D80G, Δ144, F157S, L452R, D614G, T791I, T859N, D950H	Increases	Increases	--	May decrease because of similar mutations as found in other variants			(38, 39)
B.1.525	United Kingdom/ Nigeria-December 2020	Global	A67V, Δ69/70, Δ144, E484K, D614G, Q677H, F888L	--	--	Decreases	May decrease because E484K mutation which helps evade the virus from antibodies induced by vaccines			(15, 40)
P.2	Brazil-April-2020	Global	E484K, F565L, D614G, V1176F	Increases	Increases	Decreases	Yes	5.8-fold decrease	Pfizer	(18, 38, 39, 41)
							Yes	2.9-fold decrease	Moderna	
B.1.617 B.1.617.1 B.1.617.2 B.1.617.3 (VUI-21 Apr-01; VOC-21APR-02; VUI-21APR-03)	India-February 2021	Global	**B.1.617**-L452R, E484Q, D614G. **B.1.617.1**-T95I, G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H. **B.1.617.2**- T19R, G142D, Δ156, Δ157, R158G, L452R, T478K, D614G, P681R, D950N. **B.1.617.**3- T19R, G142D, L452R, E484Q, D614G, P681R, D950N.	Increases	--	Decreases	Yes	2-fold decrease	Covaxin	(20, 21)
							There is potential decrease in neutralization of coronavirus by different vaccine for the variants like B.1.617.1, B.1.617.2 and B.1.617.3.			
B.1.1.7	United Kingdom-February 2020	Global	Δ69/70, Δ144, E484K, S494P, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H, K1191N	Increases	Increases	Decreases	Yes	No decrease	Pfizer	(12, 14, 42, 43)
							Yes	No decrease	Moderna	
P.1	Japan/ Brazil-January 2021	Global	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I	Increases	Increases	Decreases	Yes	3.8-4.8-fold decrease	Pfizer & Moderna	(24, 27, 28)
B.1.351	South Africa-October 2020		D80A, D215G, Δ241/242 /243, K417N, E484K, N501Y, D614G, A701V	Increases	Increases	--	Yes	6.4-fold decrease	Moderna	(14, 18, 44)
B.1.427	United States-June 2020	Global	L452R, D614G	Increases	Increases	Increases	Yes	2-fold decrease	Pfizer & Moderna	(32, 45)
B.1.429	United States-June 2020	Global	S13I, W152C, L452R, D614G	Increases	Increases	Increases	Yes	2-fold decrease	Pfizer & Moderna	(14, 32)

[#]**Note:** The neutralization of SARS-CoV-2 indicates the value after injection of two shots of mentioned vaccines.

tion. This is because high neutralizing titer of antibodies are found for S477N mutation comparable to D614G. However, the neutralization effect of antibodies induced by vaccine slightly decreases for E484K substitution (3.5-folds decrease in the titer) for both Pfizer-BioNTech mRNA vaccine (USA) and Moderna mRNA vaccine (USA)[9,12,13].

B.1.526 lineage led to the emergence of two more mutants/variants *viz.* B.1.526.1 & B.1.526.2.

B.1.525 Variant

The B.1.525 variant is also known as 20A/S:484K. It was first detected in United Kingdom/Nigeria in December-2020. It is mainly defined by three main mutations *viz.* E484K, Q677H and F888L. It contains many other mutations as well like A67V, Δ69/70, Δ144 and D614G[14]. The mutation which occurs at position 677 changes Gln to His. This change in amino acid leads to stronger binding of viral spike protein to human cells. It increases the transmissibility of variant as it increases the S1-S2 association stability. It was found responsible for almost 20% Covid-19 cases in Nigeria[15]. The other mutation E484K helps the virus in evading the antibody attack produced by the vaccination in human beings like for B.1.526 variant[12]. The function associated with F888L is still unknown[16].

P.2 Variant

The P.2 variant is also known as 20J. It was detected for the first time in Brazil in April-2020. The main mutations found in spike protein of P.2 variant were E484K, F565L, D614G and V1176F. E484K substitution in Brazilian variant helps SARS-CoV-2 virus in duping neutralizing antibodies produced in human body as a result of vaccination[17]. Due to this E484K substitution, P.2 variant showed significant decrease in viral neutralization by antibodies produced by both Pfizer and Moderna vaccine. The decrease was approximately 5.8 folds and 2.9 folds, respectively for Pfizer and Moderna vaccine[18].

B.1.617 Variant

B.1.617+ lineage is also known as G/452R.V3. The other name for B.1.617 variant is 20A. It was first detected in the month of October-2020. It became popular all over the world during early quarter of 2021. It created havoc in India causing large number of deaths. The main mutations found in the first variant of this group are L452R, E484Q, D614G. It is also called double mutant by the scientists as it contains both E484Q and L452R mutations in a single variant strain. The recent name given to this variant is "Delta". The latest news in India claims that it has been further mutated and now it is known as "Delta plus variant". The detailed information for delta plus variant is yet to be released. These two mutations together have made this variant more capable of evading the neutralization effect of antibodies. These antibodies could be either produced by the human body exposed to previous variants or vaccine immunized individuals[19]. There are articles authenticating this view showing decrease in neutralization effect of Pfizer mRNA-based vaccine. The other vaccine named Covaxin (Inactivated virus) synthesized in India is showing good results in vaccinated individuals but with almost 2-folds decrease in neutralization effect[20,21]. The increased infectivity of B.1.617+ lineage has been associated to the above-mentioned mutations viz. E484Q and L452R. More than 20% of the infected Covid-19 patients detected in Maharashtra (India) are found to carry this mutated variant[19].

There are three more variants belonging to this lineage viz. B.1.617.1, B.1.617.2 and B.1.617.3 with few more mutations which causes change in the spike protein.

B.1.1.7 Variant

This lineage of coronavirus was first detected in United Kingdom. It was highly transmissible and very rapidly led to its spread globally. This variant was known by many names like UK variant or British variant or even Kent variant[22]. The main mutations reported in this variant were Δ69/70, Δ144, E484K, S494P, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H and K1191N. It was found to be highly virulent leading to large number of hospitalizations in United Kingdom and all over the world[7,8,23]. It contains a very famous mutation E484K, which was found in many other variants also like South African variant. This mutation is known for evading the action of antibodies in many other variants. But the vaccine made by Pfizer and Moderna shows good results without any decrease in the neutralization property of the immunized patients' sera[9,20,21].

P.1 Variant

P.1 strain from Brazil has been classified as VOC by CDC. It is also known as 20J/501Y. V3. It showed various mutations in spike protein like L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y and T1027I. Most of these mutations in spike protein are responsible for greater binding affinity to ACE2

receptor especially K417T, E484K and N501Y[24]. These triplet mutations are also responsible for increased transmission rate and virulence[25]. It leds to widespread infection of SARS-Co-V2 in the city of Manaus and the capital of Amazonas[26]. It was able to produce around 10-folds more viral load in comparison to SARS-CoV-2-infected individuals by earlier strains. This strain was successful in infecting younger human beings without any discrimination to males and females. It was found to be almost 10-80% more lethal and was able to dupe earlier developed immunity leading to widespread reinfection. The studies show that P.1 strain also causes almost 3.8-4.8-folds decrease in neutralizing antibodies produced by Pfizer and Moderna vaccines[24,27,28].

B.1.351 Variant

It is a variant of SARS-CoV-2 popularly known as South African COVID-19 variant. It is also known by another name called 20H/501.V2. It has been classified under VOC. It was detected in South Africa in October-2020[29]. The South African COVID-19 variant showed many mutations which are important viz. D80A, D215G, Δ241/242/243, K417N, E484K, N501Y, D614G and A701V (Table I)[14]. The triplet mutations K417N, E484K and N501Y present in spike region of B.1.351 variant make it capable of binding to ACE-2 receptor. These three mutations render it to be highly transmissible and causing large number of deaths in South Africa and various other countries across the globe[29]. The mRNA-based vaccine made by Moderna showed neutralization activity against B.1.351 strain but at 6.4-fold decrease in neutralization antibody concentration.

B.1.427 Variant

This variant of SARS-CoV-2 is known as "California variant". It was also known as 20C/S:452R. It was first detected in California in June-2020[14]. It was called "home grain" strain and very quickly was held responsible for almost 90% of SARS-CoV-2 infections in the state[30]. It was placed in a category named VOC by CDC[14]. The California variant carries three main mutations in spike protein. The mutation at position 452 which changes amino acid leucine to arginine. It was found responsible for decreasing the neutralizing effect of antibodies produced either by earlier SARS-CoV-2 infection or induced by the shots of vaccine (Pfizer and Moderna)[31]. The other mutant D614G in spike protein enhances the transmissibility and virulence of the variant strain which makes it more lethal. These two mutations make this strain highly competent to infect 293T cells and human lungs carrying ACE2 receptors[32].

B.1.429 Variant

B.1.429 lineage is known as CAL.20C. This variant was detected in United States in June-2020. It was classified as VOC[14]. It has also been referred as "California variant" by scientists and even common people all over the world[30]. The main mutations present in spike protein of B.1.429 strain are S13I, W152C, L452R, D614G[14]. It was found to have approximately 20% more transmission rate than the wild type coronavirus. The high infectivity and transmission rate can be attributed to D614G and L452R mutations[32,33]. It was also held responsible for serious illness in patients with COVID-19 leading to death of many individuals in USA and many other countries[30]. The popular mRNA-based vaccines (Pfizer and Moderna) show good production of neutralizing antibodies against B.1.429 strain but almost 2-folds decrease compared to the ancestral SARS-CoV-2[32].

Results

The new SARS-CoV-2 variants rapidly dominated the COVID-19 scenario in almost all countries of the world. They were able to do so by changing themselves during the process of genome replication. During the mentioned process they undergo mutation at various positions in their spike protein *viz.* S477N, E484K, Q677H, E484Q, L452R, K417T, K417N and N501Y[12,13,18,24,25,29]. These mutations are broadly responsible for the modulating properties like transmission of the mutant strain, virulence and decrease in the neutralization capacity of the antibodies[34]. E484K mutation is mainly attributed with a property through which it escapes the host immunity. This makes the virus capable of decreasing the neutralization effect of antibodies produced by the human beings either as a result of natural SARS-CoV-2 infection or induced by vaccines. It is found in many variants like B.1.526, B.1.525, P.2, B.1.1.7, P.1 and B.1.351. Thus, it can be said that it led to many folds decrease in neutralization capacity of antibodies synthesized as a result of vaccines manufactured by the pharmaceutical companies like Pfizer and Moderna. The E484Q and L452R mutations are found in a variant originated in India (B.1.617) (double mutant). The emergence of the mentioned double mutant in India as well as oth-

er different countries of the world has considerably raised the number of SARS-CoV-2 infection. The Indian made vaccine named Covaxin (Not approved by FDA yet) has shown good results in clinical trials but 2-folds decrease in viral neutralization compared to the wild strain of SARS-CoV-2 virus has been observed[35]. The presence of the K417N+E484K+N501Y triplet mutations in B.1.351 and P.1 have made these variants almost 50% more infectious leading to widespread emergence of the virus all over the world. Additionally, it has been found that the mentioned Brazil (P.1) and South African variants (B.1.351) decreases antibody neutralization for Pfizer and Moderna vaccines almost 6-folds. Although, the currently available vaccines are working modestly but with lesser neutralization capacity and reduced efficiency[9]. Therefore, it is suggested to scale-up the vaccination drive in all the countries of the world without discrimination of economically poor or developed status.

The B.1.526 (New York variant), B.1.525 (Nigeria variant), P.2 (Brazil variant), B.1.1.7 (United Kingdom variant), P.1 (Brazil strain) and B.1.351 (South African variant) contain E484K mutation[9,12,13]. It has increased the immune escape potential of these variants leading to 3.5-6.5-folds decrease in the neutralization of antibodies produced by Pfizer and Moderna vaccines[14]. The variant named B.1.617 (known as double mutant due to E484Q and L452R changes) widely found in India[19]. It has spread to many other countries as well across the globe. These double changes or mutations have raised the infection rate and considerably decreased the neutralization capacity of the vaccine-induced antibodies. The other mutations causing problem in different countries are called triplet mutations. These deadly triplet mutations *viz.* K417N+E484K+N501Y are found in B.1.351 and P.1 variants[25]. They have increased the transmission ability of these strains by 50% leading to greater COVID-19 hospitalization, ICU admissions and deaths. These mutations have decreased the antibody neutralization of Pfizer and Moderna vaccines almost 6-folds against B.1.351 and P.1 variants[24,27,28].

Conclusions

In the last one year, nearly 19 vaccines against SARS-CoV-2 have entered clinical trials, and 9 of them got emergency use approval. However, the noticeable defeat of neutralization ability and decline in the shielding efficacy of currently available vaccine regimens suggest the potential immune escape of these SARS-CoV-2 variants. Nevertheless, the immune escape caused due to mutation dynamics of SARS-CoV-2 variants pose an unforeseeable danger to the whole world. Due to this situation, the global fast-track vaccine development and implementation strategies must be followed. Despite emergence of newly SARS-CoV-2 strains, still the currently available vaccines hold a certain level of efficacy against the variant strains. Thus, exigent rollouts of currently available vaccines to immunize a larger population is presently the finest option for managing the danger of emerging variant strains. It is recommended that the new vaccines should continuously be made and approved for future use as new variants can emerge and create havoc. Other possible strategies to tackle these variants might include, improving vaccine-induced immune response via increasing the number of doses and alternating vaccines, developing next generation vaccines such as multivalent vaccines, or nasal vaccines. These probable vaccine strategies will offer the basis for policy related decisions of R&D and regulatory authorities. Also, the isolation and sequencing of viral strains vary remarkably from country to country that affect the reliability of the generated data, which might not be the true illustration of the existing COVID-19 condition. Hence, close monitoring of genetic mutation studies must be strengthened. The genome sequencing of the circulating SARS-CoV-2 strains should be done continuously by following the standard protocol(s) in all the countries across the globe. It will help in containing the new variants rapidly by taking appropriate steps in minimal possible time.

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Authors' Contributions

Conceived and designed the study and experiments: MW AJ RKM HA EMJ KD PS SH. Performed the experiments: MW AJ RKM EMJ. Analyzed the data: MW AJ RKM.

Contributed reagents/materials/analysis tools: HA EMJ KD PS SH. Wrote the paper: MW KD SH. All authors reviewed the manuscript.

Conflicts of interest

The authors declare that they have no conflict of interests.

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